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Gamma-glutamyltransferase and risk of chronic kidney disease: a prospective cohort study

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Abbreviation: CHD, coronary heart disease; CI**,** confidence interval (CI)**;** CKD, chronic kidney disease; CVD, cardiovascular disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; HR, hazard ratio; KIHD, Kuopio Ischaemic Heart Disease; NAFLD, Non-alcoholic fatty liver disease; RDR, regression dilution ratio; SD, standard deviation; SES, socio-economic status; SBP, systolic blood pressure

ABSTRACT

Background: Elevated serum gamma-glutamyltransferase (GGT) activity has been linked with an increased risk of chronic kidney disease (CKD) in Asian populations. We aimed to assess the prospective association of serum GGT with risk of CKD in a Caucasian population.

Materials and methods: We related GGT activity to the incidence of CKD in 2,338 men aged 42-61 years of the Kuopio Ischemic Heart Disease study with normal kidney function at baseline. Repeat measurements of GGT were used to correct for within-person variability.

Results: During a median follow-up of 25.6 years, 221 men developed new-onset CKD. The age-adjusted regression dilution ratio of $\log_e$ GGT was 0.70 (95% CI: 0.64-0.75). Gamma-glutamyltransferase was log-linearly associated with risk of CKD in age-adjusted analysis. In Cox regression analysis adjusted for age, the hazard ratio (95% CIs) for CKD per standard deviation increase in $\log_e$ baseline GGT was 1.25 (1.09-1.43) which was attenuated to 1.01 (0.86-1.19) on further adjustment for several confounders.

Conclusion: Contrary to previous evidence of an independent association between elevated GGT and increased risk of CKD in Asian populations, initial evidence of an association between GGT and CKD in Caucasian men was confounded by body mass index, lifestyle factors, and lipids.

Keywords: Chronic kidney disease; cohort study; gamma-glutamyltransferase; risk factor

1. Introduction

The prevalence of chronic kidney disease (CKD) is estimated to be about 8-16% worldwide [1]. Common complications of CKD include anaemia, mineral and bone disorders, cognitive decline, end-stage renal disease, and eventually death [1]. In 2010, CKD was ranked 18th in the list of causes of the total number of global deaths, with an annual death rate of 16.3 per 100,000 [2]. Chronic kidney disease is a global public health problem and its burden is increasing worldwide. Diabetes, hypertension, and obesity are established risk factors for CKD [1]. Other known factors involved in its pathogenesis include glomerulonephritis, infectious diseases, environmental pollution, abuse of analgesics, pesticides, and herbal medications [3]. Though these leading factors explain a large proportion of the risk of CKD, its pathogenesis is still not fully established as several unknown factors appear to be involved. It is therefore of relevance to evaluate other putative risk factors that may aid our understanding of CKD development, have predictive or causal relevance, and which will guide the development of preventive strategies. Gamma-glutamyltransferase (GGT), a known index of liver injury and commonly used as a marker for excessive alcohol consumption [4], has been consistently shown to be positively related with the future risk of several chronic disease outcomes in large-scale observational cohorts [5]. Emerging evidence also suggests that GGT might also be related to the risk of CKD, however, the evidence is limited and uncertain. Targher and colleagues using data from the US National Health and Nutrition Examination Survey, found a strong and independent association between increased serum GGT and CKD [6]; however, the temporal nature of this relationship could not be established because of the cross-sectional nature of their study design. Ryu and colleagues in the first prospective evaluation of GGT and CKD, employed a cohort of 10,337 Korean male workers with normal kidney function at baseline, and demonstrated increased GGT activity to be significantly associated with an increased risk of future CKD in a nonlinear fashion [7]. The most recent prospective cohort study conducted in urban Han Chinese also showed a positive relationship between GGT and CKD incidence [8]. The prospective relationship between GGT and CKD among general Caucasian populations has not been previously investigated.

Furthermore, the long-term relevance of GGT to the risk of CKD is not known. Due to measurement errors in assays, lifestyle changes, ageing, and chronic disease, analysis using only baseline measurements of an exposure could underestimate the true strength of any aetiological association between the exposure and disease outcome (i.e. "regression dilution bias"[9]). Given that recent evidence indicates that GGT exhibits high within-person variability[10], previous studies may have under-estimated the association between GGT and CKD. In this context, we sought to evaluate in detail, the nature and magnitude of the prospective association of GGT with risk of CKD, using a population-based cohort of 2,338 Caucasian men from eastern Finland with apparently normal renal function at baseline. Serial measurements of GGT performed at 4 and 11 years after baseline in a subsample of study participants enabled quantification of within-person variability in GGT activity.

2. Materials and methods

This report was conducted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary material 1**).

2.1. Study design and participants

The present study is based on participants from the Kuopio Ischemic Heart Disease (KIHD) prospective cohort study, which was set up to investigate risk factors for cardiovascular disease (CVD) and other chronic disease outcomes. Details of study design and recruitment methods have been described in previous reports [11, 12]. Participants of the KIHD study constituted a representative sample of men aged 42-61 years who were living in the city of Kuopio and its surrounding rural communities in eastern Finland during the period of baseline examinations; which were conducted between March 1984 and December 1989. Of 3,433 potentially eligible and randomly selected men; 3,235 were found to be eligible, and of this number, 2,682 (78%) volunteered to participate; 186 provided no response to the

invitation and 367 declined to give informed consent. For the present analyses, we excluded participants with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 at baseline (n=56). The final dataset analysed comprised of 2,338 men who had complete information on GGT, relevant risk factors and markers, and CKD outcomes. The Research Ethics Committee of the University of Eastern Finland approved all study procedures which was conducted according to the Declaration of Helsinki. Each participant provided written informed consent.

2.2. Assessment of risk markers

The methods for the collection of blood specimens and measurements of lipids and biochemical analytes have been described previously [13]. In brief, participants were instructed to fast overnight, abstain from alcohol consumption for at least 3 days, and to keep away from smoking for at least 12 hours prior to the assessments. The blood samples were taken from study participants in the morning and serum samples were stored frozen at -80 °C before analyses. The kinetic method (Thermo Fisher Scientific, Vantaa, Finland) was used to measure GGT activity, with repeat measurements performed in a random subset of participants at 4 years and 11 years after the baseline measurements, as described in previous reports[10, 14, 15]. Serum C-reactive protein (CRP) was assessed with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). The glucose dehydrogenase method (Merck, Darmstadt, Germany) was used to measure fasting plasma glucose (FPG). Participants completed self-administered health and lifestyle questionnaire for the assessment of age, smoking, alcohol consumption, socio-economic status (SES), baseline diseases, and medical history[13]. Energy expenditure of physical activity was assessed using the validated KIHD 12-month leisure-time physical activity questionnaire [16, 17]. Estimated glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[18] using the formula:

$$eGFR = 141 \times (\text{creatinine in mg/dl} / 0.9)^{-1.209} \times 0.993^{Age}$$

2.3. Ascertainment of incident chronic kidney disease

In the KIHD study, participants are under continuous surveillance for the development of new outcomes including CKD cases. All incident CKD cases that occurred from study entry to 2014 were included and no losses to follow-up were recorded. Chronic kidney disease outcomes were collected from the National Hospital Discharge Register data by computer linkage and a comprehensive review of available hospital records, wards of health centres, health practitioner questionnaires, and medico-legal reports. Chronic kidney disease was defined as kidney damage or glomerular filtration rate lower than 60 mL/min per 1.73 m^2 for 3 months or longer.

2.4. Statistical analyses

Prospective cohort analyses All skewed variables (GGT, CRP, and triglycerides) underwent log transformation to approximate normal distributions. Baseline characteristics were presented as means (SD) for continuous variables and percentages for categorical variables. Cox proportional hazard regression models were used to conduct time-to-event analyses after confirming assumptions of proportionality of hazards using Schoenfeld residuals [19]. We quantified and corrected for within-person variability in values of GGT using adjusted regression dilution ratios (RDRs) which were calculated by regressing available repeat GGT measurements on baseline values [20], as described in detail previously. To assess the shape of the relationship between GGT and CKD risk, hazard ratios (HRs) and confidence intervals (CIs) were calculated within quartiles of baseline GGT values using floating absolute risks, and these were plotted against mean values within each GGT quartile. This was to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile). As the association showed a linear shape in age-adjusted analysis with a relatively flat risk of CKD in multivariate analysis, GGT was modelled continuously [per 1 standard deviation (SD) increase] and as categories (quartiles) defined according to its baseline distribution. The HRs were adjusted progressively for (i) age; (ii) plus body mass index (BMI), systolic blood pressure (SBP), history of

hypertension, prevalent coronary heart disease (CHD), smoking status, history of diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-C), alcohol consumption, and eGFR; and (iii) plus total energy intake, SES, physical activity, and CRP. We performed subgroup analyses using interaction tests to assess statistical evidence of any differences in hazards across categories of pre-specified individual level characteristics. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 2,338 participants included in the present analysis are summarised in **Table 1**. The mean age of study participants was 53 (SD, 5) years. Median (interquartile range) GGT value was 20 (15-33) U/L and the mean (SD) of $\log_e$ GGT was 3.13 (0.65) U/L. Except for alcohol consumption, BMI, blood pressure, glucose, and CRP, baseline characteristics were generally similar across quartiles of serum GGT. Levels of alcohol consumption, BMI, blood pressure, fasting glucose, and CRP were higher in participants in the top quartile of GGT values.

3.2. Correction for within-person variability in GGT

In a random sample of 711 participants, serial measurements of GGT were taken 4 and 11 years after the baseline measurements, which yielded a total of 1,422 repeat measurements of GGT. Overall, the age-adjusted RDR of loge GGT was 0.70 (95% CI: 0.64 to 0.75), which suggests that the association of GGT with CKD risk using baseline measurements of GGT could under-estimate the risk by [(1/0.70)-1]*100 = 43%.

3.3. Gamma-glutamyltransferase and risk of chronic kidney disease

During a median follow-up of 25.6 (interquartile range, 17.6-27.8) years, 221 CKD cases (annual rate 4.29/1,000 person-years at risk; 95% CI: 3.76 to 4.89) were recorded. Cumulative hazard curves did not show a significant greater risk of new-onset CKD among males in the top quartile of GGT values compared to those in the bottom quartile ($P = 0.187$ for log-rank test; **Figure 1**). In age-adjusted analysis, a log-linear association was observed between GGT and risk of CKD, which became relatively flat on further adjustment for established risk factors (BMI, SBP, history of hypertension, prevalent CHD, smoking status, history of diabetes, total cholesterol, HDL-C, alcohol consumption, and eGFR (**Supplementary material 2**). The age-adjusted HR for CKD per 1 SD increase in GGT was 1.25 (95% CI: 1.09 to 1.43), which was attenuated to 1.04 (95% CI: 0.89 to 1.22) on further adjustment for established risk factors. The association remained absent on additional adjustment for total energy intake, SES, physical activity, and C-reactive protein 1.01 (95% CI: 0.86 to 1.19). Alternatively, comparing the top versus bottom quartiles of GGT values, the corresponding adjusted HRs were 1.59 (95% CI: 1.11 to 2.29), 0.97 (95% CI: 0.64 to 1.47), and 0.92 (95% CI: 0.60 to 1.40) respectively (**Table 2**). The corresponding adjusted HRs per 1 SD change in usual $\log_e$ GGT values were 1.37 (95% CI: 1.12 to 1.66), 1.06 (95% CI: 0.84 to 1.32), and 1.02 (95% CI: 0.81 to 1.29) respectively (**Table 2**). There was no statistical significant evidence of effect modification by levels or categories of several clinically relevant characteristics and other risk markers (P for interaction ≥ 0.10 for each; **Figure 2**).

4. Discussion

In this large-scale population-based study of middle-aged Finnish men with apparently normal kidney function at baseline, we observed a log-linear association between GGT and risk of CKD disease in age-adjusted analysis; however, the association was less robust on further adjustment for body mass index, blood pressure, lifestyle factors, history of diabetes, and serum lipids. The statistically non-significant association remained generally consistent across several clinically relevant subgroups.

There are limited published data on the association of GGT with CKD risk. Though a previous cross-sectional analysis has shown GGT to be associated with albuminuria in a Chinese population;[21] to our knowledge, only two large-scale prospective studies conducted among Asian populations have reported on the associations between GGT and risk of CKD to date [7, 8] (**Supplementary Material 3**). Whiles Ryu et al. in their analysis of men without a prevalent history of hypertension or diabetes, demonstrated a nonlinear relationship to the association between GGT and CKD risk [7]; the findings by Shen et al. suggested a linear shape to the relationship, but the association was only statistically significant for men [8].

Limited evidence suggests an independent association between GGT and risk of CKD and a number of potential mechanisms have been hypothesized to underlie the association. Ryu and colleagues speculated that alcohol consumption, liver disease, obesity, insulin resistance, and low-grade inflammation could underlie the association [7]. However, the authors suggested that it was unlikely that these were the main mechanisms underlying the association, as those variables were carefully accounted for in their fully-adjusted multivariate analyses. Given that GGT has pro-oxidant properties [22] and is a source of reactive oxygen species (ROS), it was further suggested GGT might contribute to the pathogenesis of CKD via mechanisms related to oxidative stress [22]. Renal ROS has been reported to cause vasoconstriction of renal vasculature, which leads to sodium retention and subsequently renal damage [23, 24]. In a recent review of the link between non-alcoholic fatty liver disease (NAFLD) and CKD, the authors postulated that the origins for this relationship were via pathways such as atherogenic dyslipidemia, dysglycemia, and the release of pro-inflammatory, pro-coagulant, and pro-fibrogenic factors, which cause kidney damage [25]. Given the strong relationship between NAFLD and GGT activity, NAFLD may be the underlying pathology in the relationship between GGT and CKD. Our null findings are at odds with previous reports and several reasons could account for the conflicting results. First, the current study may not have had adequate power due to its relatively small sample size and low event rate compared with previous studies. Second, whiles the current study had a long follow-up duration of over 20 years, the

follow-up period for previous studies were shorter. Given the long-term follow-up of our cohort, the phenomenon of regression dilution may have underestimated the true association between GGT and CKD risk.[26, 27] Indeed, analysis of repeat measurements of GGT in a subsample of participants suggested that using baseline measurements of GGT could under-estimate the risk by about 40%. Third, there may be true differences, due to differences in study population characteristics such as age, race or genetic background. For instance, the current study was employed in middle-aged Caucasian men who were genetically homogenous, whiles the two previous studies were based in Asian populations who were younger.[7, 8] Our study adds to the growing literature on a potential role of GGT in the development of several chronic diseases [5, 15, 28-30]. Whether GGT may be a putative risk factor for CKD risk or a marker of underlying CKD in Caucasian populations, is still uncertain. The overall evidence on the relationship between GGT and CKD is indeed limited; therefore, further large-scale studies are warranted to investigate the associations and mechanistic studies are also needed to investigate the aetiopathogenic pathways postulated to underlie the GGT-CKD association.

Our analysis used a large-scale population-based prospective cohort design with inclusion of men who were representative of the general population with apparently normal kidney function at study entry. There was a high response rate and follow-up was complete for all participants. Other strengths of the current analysis include the long follow-up period of over 20 years; comprehensive analysis with adjustment for a broad panel of lifestyle, socioeconomic factors, and biochemical markers which allowed adequate adjustment for several risk factors; assessment of the shape of the association and stratified analyses by several clinical relevant characteristics. Repeat measurements of GGT made within a random subset of individuals over time after baseline were available, enabling correction for within-person variability in GGT activity over the long period of follow-up. However, these were made in only a small sample of participants. Studies with repeat measurements of serum GGT in larger samples are still needed to assess its variability in greater detail. Some limitations deserve mention and these include: (i) the findings cannot be generalised to women and other populations; (ii) the potential for residual confounding

which is always a limitation for observational studies of this nature; and (iii) the relatively small number of CKD cases available.

Contrary to previous evidence of an independent association between elevated GGT and increased risk of CKD in Asian populations, initial evidence of an association between GGT and CKD in middle-aged Caucasian men was confounded by body mass index, blood pressure, lifestyle factors, and lipids. Further research is needed to evaluate the prospective association between GGT and CKD risk, especially in women.

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Conflicts of interest

None to declare.

Authorship

SKK researched data, analyzed data and wrote the manuscript. SKK and JAL contributed to data collection, reviewed and edited the manuscript. SKK is the guarantor and had full access to all the data in the study and takes responsibility for the integrity of the data and the decision to submit and publish the manuscript.

Ethics

This study protocol was evaluated by the ethical committee of our institution. A written consent was obtained from each patient evaluated in this study.

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Table 1 Baseline Participant Characteristics by Quartiles of Gamma-glutamyltransferase

	Overall (N=2,338) Mean (SD) or n (%) or median (IQR)	**Quartile 1 (range 5-15 U/L) Mean (SD) or n (%) or median (IQR)**	**Quartile 2 (range 16-20 U/L) Mean (SD) or n (%) or median (IQR)**	**Quartile 3 (range 21-33 U/L) Mean (SD) or n (%) or median (IQR)**	**Quartile 4 (range ≥ 34 U/L) Mean (SD) or n (%) or median (IQR)**
GGT (U/L)	20 (15-33)	12 (11-14)	18 (16-19)	26 (23-29)	48 (40-71)
Questionnaire/Prevalent conditions					
Age at survey (years)	53.1 (5.0)	53.2 (5.2)	53.4 (4.8)	53.3 (4.8)	52.6 (5.1)
Alcohol consumption (g/week)	75.1 (135.5)	38.6 (69.8)	57.2 (85.4)	75.9 (171.0)	135.6 (165.7)
Total energy intake, kJ/day	9,886 (2,589)	10,387 (2,577)	9,859 (2,594)	9,745 (2,574)	9,437 (2,521)
Socioeconomic status	8.58 (4.23)	8.82 (4.18)	8.54 (4.27)	8.32 (4.26)	8.58 (4.23)
History of diabetes	92 (3.9)	8 (1.2)	15 (3.1)	32 (5.3)	37 (6.7)
Current smokers	742 (31.7)	193 (27.9)	153 (31.6)	202 (33.2)	194 (35.1)
History of hypertension	706 (30.2)	131 (18.9)	143 (29.5)	198 (32.6)	234 (42.3)
History of CHD	589 (25.2)	148 (21.4)	109 (22.5)	145 (23.9)	187 (33.8)
Physical measurements					
BMI (kg/m^2)	26.9 (3.6)	25.4 (2.9)	26.6 (3.3)	27.1 (3.3)	28.8 (3.9)
SBP (mmHg)	134 (17)	129 (16)	134 (16)	135 (16)	139 (18)
DBP (mmHg)	89 (11)	85 (10)	88 (10)	89 (10)	92 (11)
Physical activity (kj/day)	1,541 (1,485)	1,462 (1,230)	1,634 (1,684)	1,554 (1,627)	1, 543 (1,426)
Lipid markers					
Total cholesterol (mmol/l)	5.92 (1.10)	5.77 (1.12)	5.91 (1.09)	6.02 (1.14)	6.01 (1.01)
HDL-C (mmol/l)	1.30 (0.30)	1.33 (0.29)	1.29 (0.29)	1.29 (0.31)	1.28 (0.31)
Triglycerides (mmol/l)	1.10 (0.80-1.55)	0.95 (0.71-1.29)	1.06 (0.78-1.47)	1.16 (0.83-1.60)	1.33 (0.94-1.89)
Metabolic, renal, and inflammatory markers					
Fasting plasma glucose (mmol/l)	5.36 (1.29)	5.13 (0.69)	5.26 (1.09)	5.35 (1.21)	5.77 (1.87)
Serum creatinine (µmol/1)	88.3 (11.6)	87.4 (11.1)	88.7 (11.4)	88.7 (11.7)	88.7 (12.4)
Estimated GFR ($ml/min/1.73\ m^2$)	87.8 (16.5)	88.6 (15.2)	87.0 (14.5)	87.2 (15.5)	88.2 (20.2)
CRP (mg/l)	1.28 (0.71-2.46)	0.87 (0.54-1.69)	1.19 (0.74-2.13)	1.49 (0.79-2.69)	1.85 (1.04-3.77)

BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase

HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure;

Table 2 Association of Serum GGT and Chronic Kidney Disease

Serum GGT (U/L)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline GGT							
Per 1 SD increase	221 / 2,338	1.25 (1.09 to 1.43)	0.002	1.04 (0.89 to 1.22)	0.630	1.01 (0.86 to 1.19)	0.877
Q1 (5-15)	63 / 692	ref		ref		ref	
Q2 (16-20)	44 / 485	1.08 (0.73 to 1.59)	0.696	0.90 (0.61 to 1.34)	0.615	0.88 (0.59 to 1.31)	0.529
Q3 (21-33)	58 / 608	1.18 (0.83 to 1.69)	0.352	0.96 (0.66 to 1.39)	0.817	0.91 (0.62 to 1.32)	0.614
Q4 (≥ 34)	56 / 553	1.59 (1.11 to 2.28)	0.012	0.97 (0.64 to 1.47)	0.903	0.92 (0.60 to 1.40)	0.704
Usual GGT*							
Per 1 SD increase	221 / 2,338	1.37 (1.12 to 1.66)	0.002	1.06 (0.84 to 1.32)	0.630	1.02 (0.81 to 1.29)	0.877
Q1 (5-15)	63 / 692	ref		ref		ref	
Q2 (16-20)	44 / 485	1.12 (0.64 to 1.93)	0.696	0.87 (0.49 to 1.52)	0.615	0.83 (0.47 to 1.47)	0.529
Q3 (21-33)	58 / 608	1.27 (0.76 to 2.12)	0.352	0.94 (0.55 to 1.59)	0.817	0.87 (0.51 to 1.49)	0.614
Q4 (≥ 34)	56 / 553	1.93 (1.15 to 3.24)	0.012	0.96 (0.53 to 1.74)	0.903	0.89 (0.49 to 1.62)	0.704

CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;
*, indicates correction for within-person variability in values of GGT, that is, the extent to which an individual's GGT measurements vary around a long-term average value ("usual GGT values")

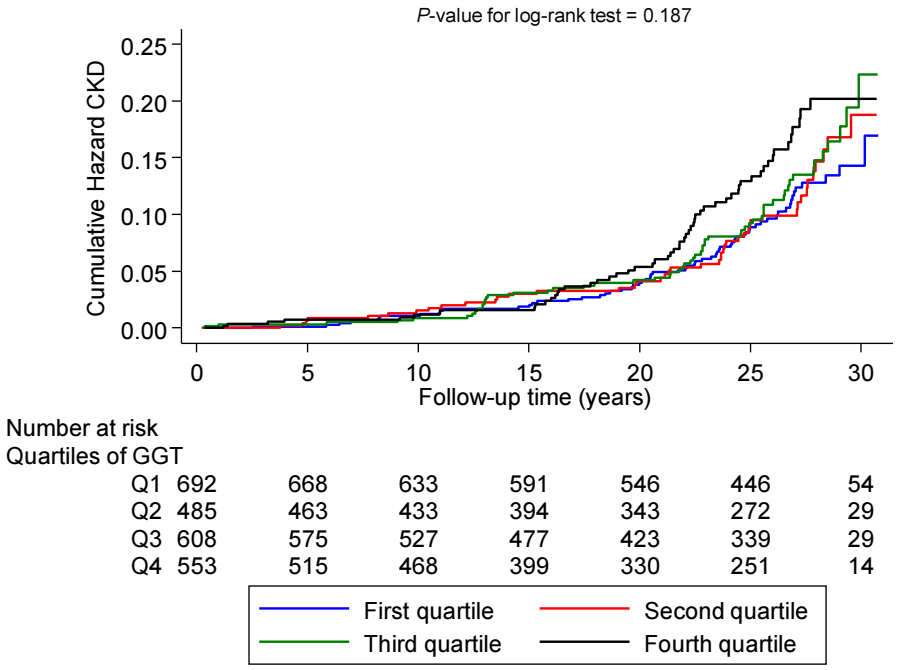
Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and estimated glomerular filtration rate

Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein

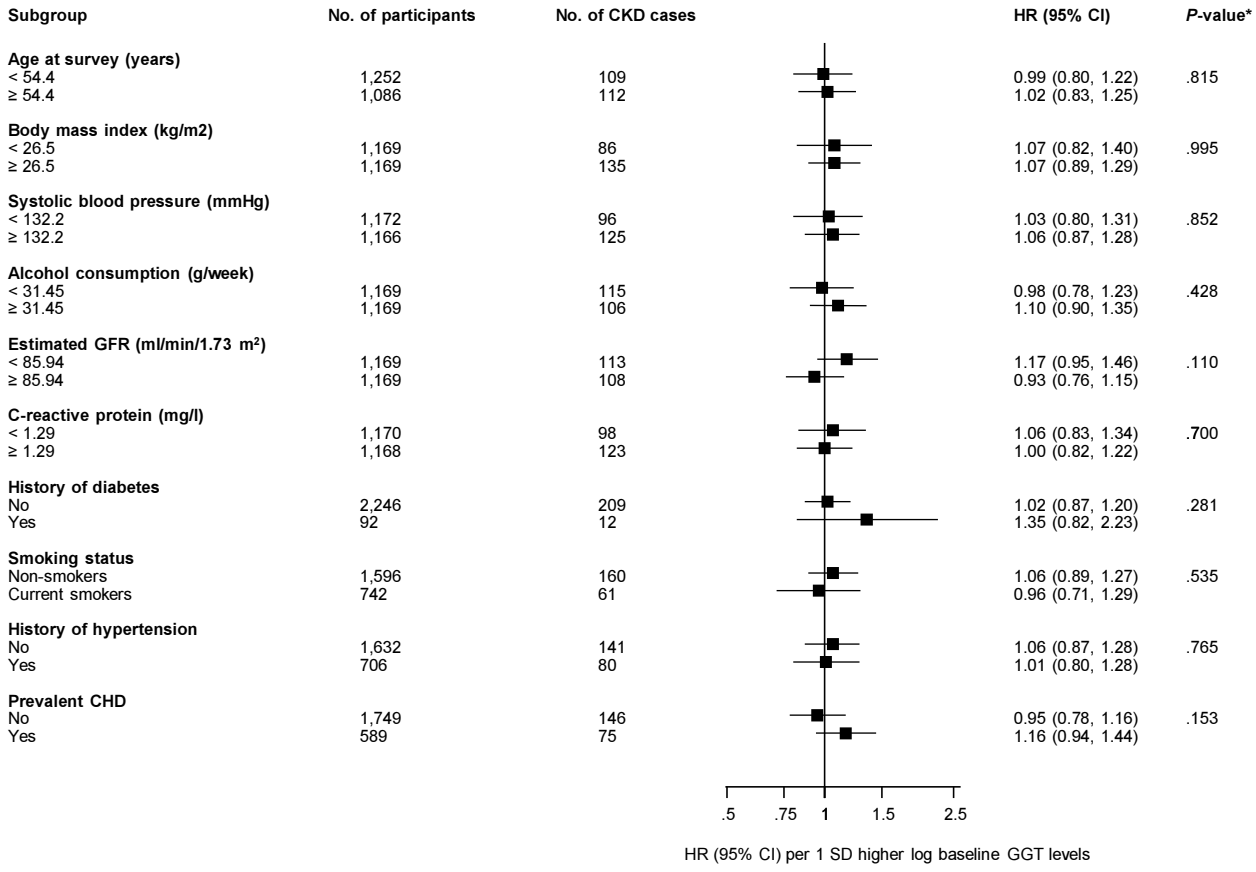
Figure legends

Figure 1. Cumulative hazard curves for chronic kidney disease by quartiles of gamma-glutamyltransferase



CKD, chronic kidney disease; Q, quartile

Figure 2. Hazard ratios for baseline values of gamma-glutamyltransferase and chronic kidney disease risk by several participant level characteristics



Hazard ratios are adjusted for age, body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and estimated glomerular filtration rate; CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HR, hazard ratio; SD, standard deviation; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, alcohol consumption, estimated glomerular filtration rate, and C-reactive protein are median values.